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THE PATENTS ACT, 1970

It is hereby certified that annexed hereto is a true copy of Application, Complete Specification, Abstract & Drawing of the extract of Patent Application No.152/MAS/2003, dated 26/02/2003 by Orchid Chemicals & Pharmaceuticals Ltd., having its registered office at 1, 6th Floor, Crown Court, 34, Cathedral Road, Chennai 600 086, Tamil Nadu, India.

.....

.....**In witness thereof**

I have hereunto set my hand

Dated this the 9th day of December 2003
18th day of Agrahayana, 1925(Saka)

M.S. Venkataraman

(M.S. VENKATARAMAN)
ASSISTANT CONTROLLER OF PATENTS & DESIGNS

PATENT OFFICE BRANCH
GOVERNMENT OF INDIA
Guna Complex, 6th Floor, Annex.II
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FORM 1

THE PATENTS ACT, 1970

APPLICATION FOR GRANT OF A PATENT (Section 5(2), 7and Rule 33A)

We, Orchid Chemicals & Pharmaceuticals Ltd., an Indian company having its registered office at 1,6th Floor, Crown Court, 34, Cathedral Road, Chennai - 600 086, TN, India hereby declare

1.(a) that we are in possession of an invention titled **Novel amorphous hydrate of a cephalosporin antibiotic and a process for its preparation**

(b) that the complete specification relating to this invention is filed with this application.

(c) that there is no lawful ground of objection to the grant of a patent to us.

2. further declare that the inventors for the said invention are

1. Pandurang Balwant Deshpande
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2. Bhausaheb Pandharinath Khadangale
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Tamilnadu, INDIA

3. that all belonging to India and citizens of India

4. that we are the assignee of the true and first inventors

5. that our address for service in India is as follows;

Dr. C. B. Rao
Orchid Chemicals & Pharmaceuticals Ltd.,
1,6th Floor, Crown Court,
34, Cathedral Road, Chennai - 600 086, TN, India

6. We, the true and first inventors for this invention declare that the applicant herein is our assignee

(Signed) _____ (Signed) _____
Pandurang Balwant Deshpande
Bhausaheb Pandharinath Khadangale

(Signed) _____
Chandrasekaran Ramasubbu

7. that to the best of our knowledge, information and belief, the fact and matters stated herein are correct and that there is no lawful ground of objection to the grant of patent to us on this application

8. following are the attachments with the application

(a) complete specification (23 pages, in triplicate)

(b) abstract of the invention (1 page, in triplicate)

(c) drawings of the invention (1 page, in triplicate)

(d) fee Rs. 5000.00 (five thousand rupees only) in cheque bearing No. 219882 dated December 10, 2002, drawn on ICICI bank, Chennai.

We request that a patent may be granted to us for the said invention

Dated this twenty fifth (25th) day of February 2003

(Signed) _____
Dr. C. B. Rao
Dy. Managing Director
Orchid Chemicals & Pharmaceuticals Ltd

To,
The Controller of Patents
The Patents Office Branch, Chennai.

FORM 2

THE PATENTS ACT, 1970

COMPLETE SPECIFICATION

(SECTION 10)

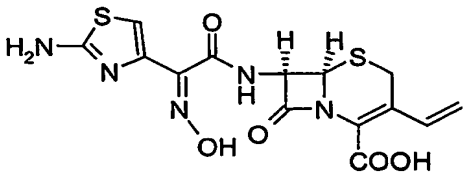
Novel amorphous hydrate of a cephalosporin antibiotic and a process for its preparation

Orchid Chemicals & Pharmaceuticals Ltd.
an Indian Company having its registered office at
1,6th Floor, Crown Court,
128, Cathedral Road
Chennai - 600 086, TN, India

The following specification describes the nature of the invention and the manner in which it has to be performed :

Field of the Invention

The present invention relates to a novel amorphous hydrate of a cephalosporin antibiotic. More particularly, the present invention relates to novel amorphous monohydrate of cefdinir of the formula (I).



(I)

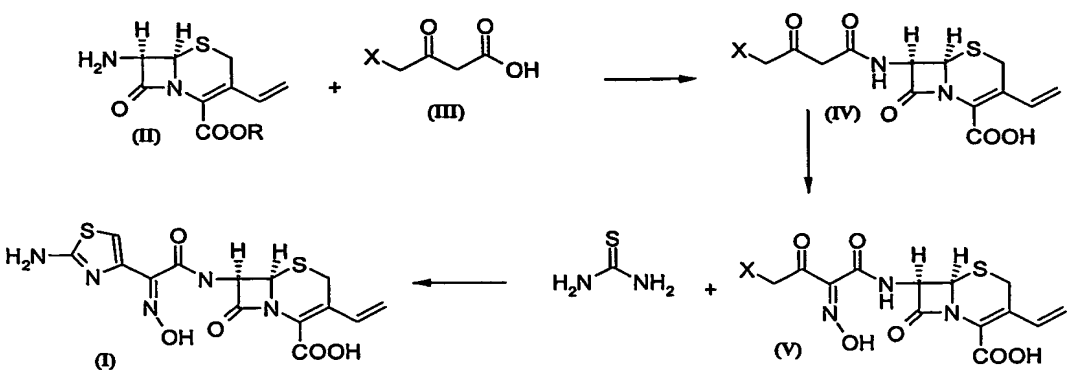
The present invention also provides a process for the preparation of the novel amorphous monohydrate of cefdinir of formula (I).

The present invention also provides new salts of compound of formula (XIV) and a process for the preparation of cefdinir using the new salts.

Background of the Invention

Cefdinir is a third generation cephalosporin antibiotic for oral administration and has a broader antibacterial spectrum over the general gram positive and gram negative bacteria, especially against *Streptococci,* than other antibiotics for oral administration.

In view of the vital antibiotic activities of cefdinir of the formula (I), various methods of preparation were reported. Cefdinir is for the first claimed in US patent No. 4,559,334 and the nature of the product that is disclosed in this patent is described as crystalline like amorphous in subsequent US patent (US 4,935,507). This patent also discloses a process for the preparation of cefdinir as depicted in the Scheme I.



Scheme I

In the disclosed process, 7-amino-3-vinyl-3-cephem-4-carboxylic acid ester where R represents a conventional carboxy protecting group, is acylated with the reactive ester of haloacylacetic acid, which was converted to its oxime, followed by cyclization with thiourea and deprotection of the ester group to afford cefdinir. The product obtained by the process described in examples 14 and 16 is approximately 80-85 % pure. The cyclization step suffers from poor yield and affords brownish color of the thiazole derivative, which subsequently affords cefdinir, but quality and yield were inferior. Further, owing to the fact that the expensive 7-amino-3-vinyl-3-cephem-4-carboxylic acid is carried through four steps, cost of producing cefdinir is high.

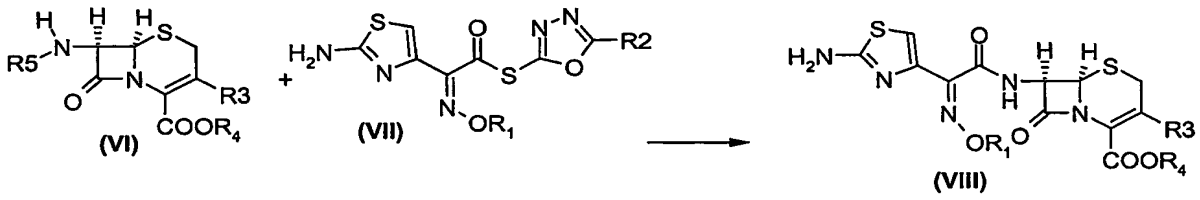
US patent number 4,935,507 claims the novel crystalline form of the cefdinir syn-isomer and a process for preparing the same. The X-ray crystallography data given in this is as given in the following table:

2 θ ° Values	Relative Intensity
14.7	76
17.8	56
21.5	100
22.0	70
23.4	38

24.4	80
28.0	40

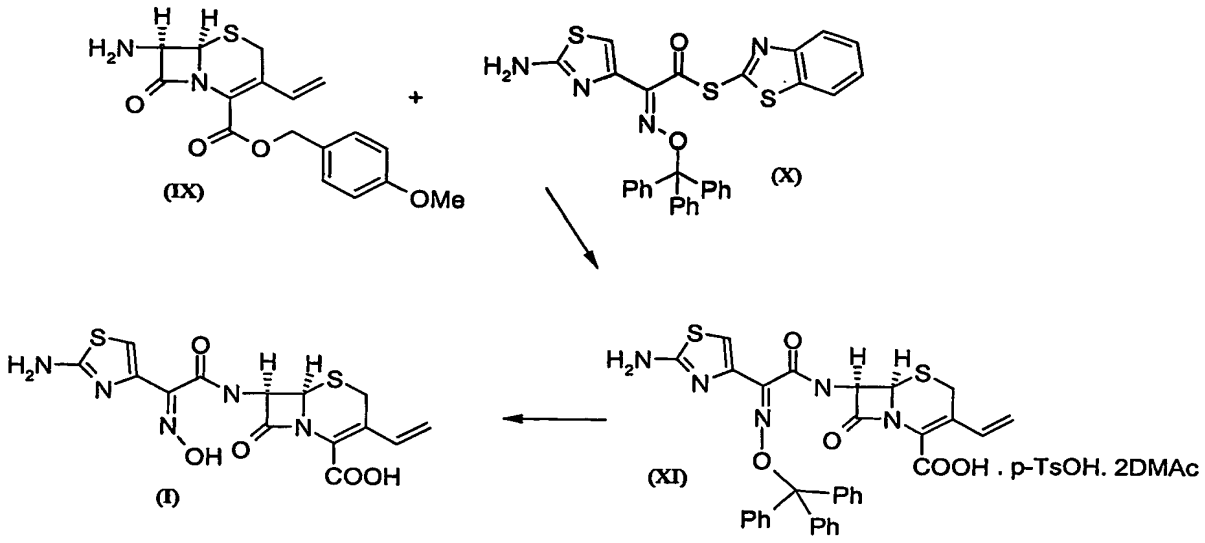
The crystalline form (Crystal A) of US 4,935,507 is prepared from the syn-isomer prepared according to the procedures described in Examples 14 and 16 of US 4,559,334.

In our US patent No. 6,388,070, we disclosed a process for preparing a compound of formula (VIII), wherein, R_1 represents H, trityl, etc., R_2 represents H, phenyl, etc., R_3 represents CH_3, CH=CH, etc., R_4 is H or a salt or a carboxylic protecting group; R_5 is H or trimethylsilyl; comprising acylating the compound of formula (VI) with compound of formula (VII) in the presence of an organic solvent, organic base and a silylating agent at a temperature in the range of -10 °C to +30 °C. The reaction is shown in scheme II below :



Scheme II

US patent No. 6,093,814 discloses a process for the preparation of cefdinir and its intermediate as represented in the Scheme III:



Scheme III

In this process p-methoxybenzyl 7-amino-3-vinyl-3-cephem-4-carboxylate is condensed with 2-mercaptobenzothiazolyl (Z)-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate in N,N-dimethyl acetamide, and the product obtained was treated with p-toluenesulfonic acid in the presence of a mixture of diethyl ether and methanol to get crystalline 7-[(2-amino-4-thiazolyl)-2-(Z)-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid.pTSA.2DMAc solvate. This process utilizes highly volatile, low-boiling and therefore industrially-not-preferred solvent, diethyl ether, for crystallizing out the above solvate. In addition, the quantity of the low-boiling solvent used is also very high ranging from 60-100 volumes, thereby adding hazard to the operations. Added to this is the fact that the recovery of these solvents from their mixture is not straight-forward.

US patent No. 6,350,869 discloses the purification of impure cefdinir through the preparation of N,N-dicyclohexylamine salt of 7-[2-amino-4-thiazolyl-2-(z)-hydroxyimino acetamido]-3-vinyl-3-cephem-4-carboxylic acid and subsequent hydrolysis to get pure cefdinir. This process requires the preparation of crude

cefdinir, conversion to N,N-dicyclohexylamine salt and then hydrolysis of the salt to get pure cefdinir, and therefore the overall yield is not attractive.

US patent No. 6,350,869 also emphasizes that cefdinir is unstable in the presence of other amines, with which, it gets heavily degraded. In addition, Yoshihiko Okamoto et al. (J. Pharm. Sci. Vol. 8S(9), 976, **1996**) report that cefdinir may be unstable under basic environment.

Crystalline cefdinir has limitations in formulation development as it cannot be developed into tablets.

Considering the foregoing limitations, we undertook an investigation in our lab to develop a product which is easy to handle and convenient to develop a dosage which is easily absorbable. We also parellely undertook an investigation to identify a process, which involves (i) less number of steps, (ii) the direct isolation of cefdinir, with out the need to prepare crude cefdinir in an additional step. This would permit commercializing the production of high-pure cefdinir with industrial-friendly solvent, which can further be recovered for recycling.

Objectives of the Invention

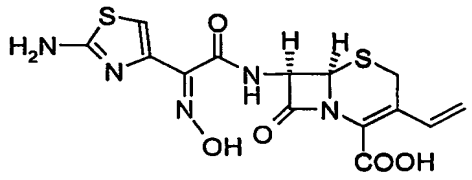
The main objective of the present invention is to provide a novel amorphous monohydrate of cefdinir which has very good bioavailability and useful in developing different dosage forms.

Another objective of the present invention is to provide a commercially viable process for the preparation novel amorphous monohydrate of cefdinir of the formula (I), which would be easy to implement on manufacturing scale.

Yet another objective of the present invention is to provide new salts of formula (XIV), which are insoluble and stable throughout the process of producing the cefdinir and a process for the preparation of cefdinir using these new salts.

Summary of the Invention

Accordingly, the present invention provides a novel amorphous monohydrate of cefdinir of the formula (I)



(I)

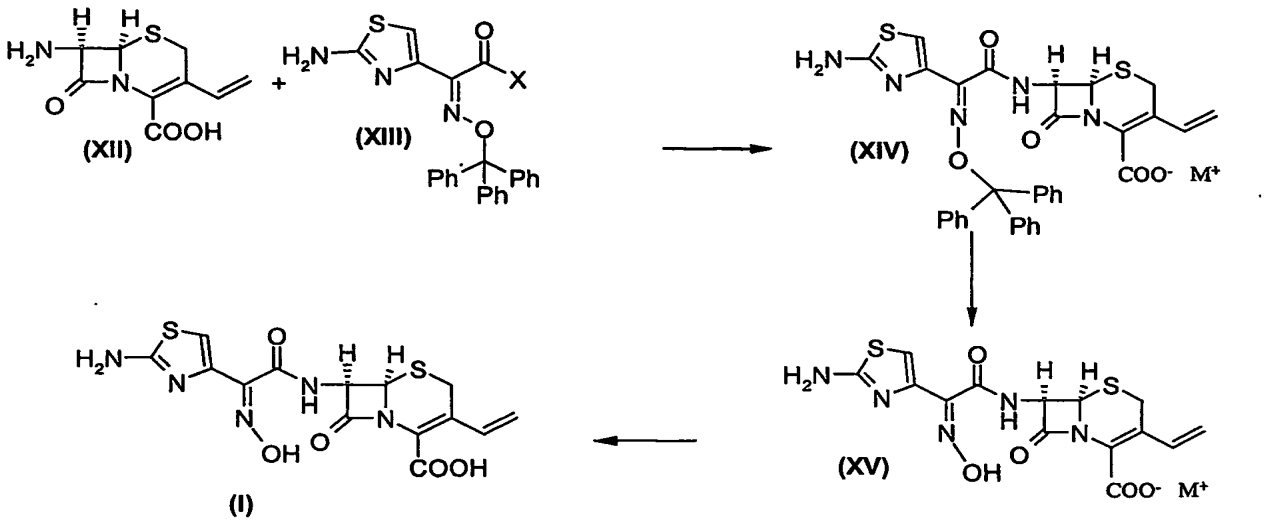
The present invention also provides a process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I), which comprises the steps of:

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (XII) with compound of the formula (XIII) wherein X represents an activating group in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (XIV), wherein M^+ is a counter ion,

ii) deprotecting the compound of formula (XIV) to produce compound of formula (XV) wherein M^+ is a counter ion in the presence of an organic solvent and a base at a temperature in the range of room temperature to 80 °C and

iii) hydrolyzing the compound of the formula (XV) using an acid at low temperatures in the range of –40 to 0 °C in the presence of an organic solvent to produce novel amorphous monohydrate of cefdinir of the formula (I).

The reaction is shown in scheme-IV below :

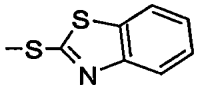
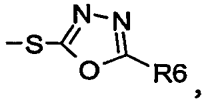
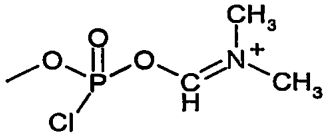
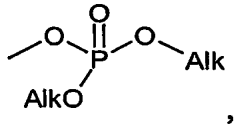
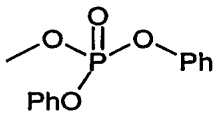


Scheme IV

Description of Figures

Figure 1 : Comparison of powder XRD pattern of the sample prepared according to US 4,935,507 and the sample prepared according to example 1 and example 2.

Detailed description of the invention

In an embodiment of the present invention, the activation group represented by X is selected from ester, thioester, halogen atom such as chlorine, bromine, iodine,  ,  ,  ,  ,  , where R_6 represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl or a phenyl group; Alk group represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl.

In an embodiment of the present invention, the counter ion represented by M is selected from sodium, potassium, lithium, magnesium, ammonium, dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine and the like.

In an another embodiment of the present invention, the tertiary amine used in step (i) is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine, trimethylamine and the like.

In yet another embodiment of the present invention, the organic solvent used in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

In yet another embodiment of the present invention, the base used in step (i) and step (ii) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, ammonium acetate, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine, N,N-diisopropylamine, and the like.

In yet another embodiment of the present invention, the organic solvent used in step (ii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

In another embodiment of the present invention, the acid employed in step (iii) is selected from HCl, sulfuric acid, formic acid, acetic acid, aromatic/aliphatic sulfonic acids such as benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid, triflic acid, and the like.

In yet another embodiment of the present invention, the organic solvent used in step (iii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water and the like or mixtures thereof.

In yet another embodiment of the present invention, the compound of formula (I) obtained is a syn isomer.

The present invention is based on the observation that rapid cooling of the aqueous solvent solution of cefdinir to low temperatures and adding the acid rapidly produces amorphous cefdinir. The technique can be achieved either by cooling the aqueous solvent solution to low temperatures and adding the acid rapidly to adjust the pH to precipitate the amorphous product or adding the acid to adjust the pH and rapidly cooling the resultant solution to precipitate the amorphous product.

In yet another embodiment of the present invention, the hydrolysis in step (iii) is carried out by cooling the aqueous solvent solution to low temperatures and adding the acid rapidly to adjust the pH to precipitate the amorphous cefdinir.

In yet another embodiment of the present invention, the hydrolysis in step (iii) is carried out by adding the acid to adjust the pH and rapidly cooling the resultant solution to precipitate the amorphous cefdinir.

The foregoing technique has been found to be markedly attractive, both from commercial point of view, as well as from manufacturing viewpoint and affords good quality of amorphous cefdinir of the formula (I).

Many other beneficial results can be obtained by applying disclosed invention in a different manner or by modifying the invention with the scope of disclosure.

The present invention is illustrated with the following examples, which should not be construed as limiting to the scope of the invention.

Example 1

Step (i)

Preparation of (2-mercapto-5-phenyl-1,3,4-oxadiazolyl)-(Z)-2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate

To an ice-cold suspension of (Z)-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetic acid (25 gm) in tetrahydrofuran (200 ml), triethylamine (10 gm) was added dropwise over 10 minutes at 0-5 °C. Bis-(2-oxo-oxazolidinyl)phosphinic chloride (15.4 gm) was added and stirred for one hour at 0-5 °C. To the reaction mixture 2-mercapto-5-phenyl-1,3,4-oxadiazole (9.8 gm) and triethylamine (5.0 gm) was added dropwise over 15 minutes and stirred at 0-5 °C for 6 – 7 hours. After completion of reaction, chilled water (500 ml) was added at 10-20 °C in 30 – 40 minutes and stirred at 20 °C for 2 hours. Then the slurry was cooled to 5-10 °C and stirred at this temperature for 45 minutes. The product thus obtained was filtered washed with water (100 ml) and dried at 30-35 °C for 4-5 hours to yield the title compound (50 gm, water content is 40%).

Step (ii)

Preparation of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (25 gm) and (2-mercapto-5-phenyl-1,3,4-oxadiazolyl)-(Z)-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate (155 gm, water content is 40 %) in N,N-dimethylacetamide (150 ml), triethylamine (23 gm) was added drop-wise at 10±2 °C over 30-45 minutes and the resulting mixture was stirred at 20±2 °C for 6-8 hours. The reaction was monitored by HPLC. After completion of the reaction, tetrahydrofuran (125 ml), 10% sodium chloride solution (250 ml) and ethyl acetate (250 ml) were added at 25 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (250 ml). To the aqueous layer, ethyl acetate (500 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl in 30 min. The

layers were separated and to the ethylacetate layer, 12 % (w/v) methanolic potassium hydroxide solution (60 ml) was added dropwise in 30 min at 25 °C, and stirred for 45 min. The resulting slurry was filtered, washed with ethyl acetate (150 ml) followed by acetone (150 ml) and dried at 30-35 °C under vacuum to obtain the title compound (45 gm, HPLC Purity >99.0%).

Step (iii)

Preparation of ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate

To a clear solution of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (250 gm) in aqueous acetonitrile (625 ml, 2:3), a solution of trimethylchlorosilane (94 gm) in acetonitrile (125 ml) was added drop wise at 60-65 °C and the temperature was maintained at 65-68 °C for 33 minutes. Chilled acetone (2000 ml) having temperature -10 °C was added to the reaction mixture to reduce the temperature to 30 - 35 °C. A methanolic solution of ammonium acetate (93 gm, 100 ml) was added drop wise while cooling. The resulting mixture was diluted with acetone (3000 ml), cooled to 10 °C and stirred for 30 minutes at 10 ± 2 °C. The crystals thus obtained were filtered, washed with acetone and dried at 40-45 °C under vacuum to get ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (207 gm, HPLC quality 94.9 %).

Step (iv)

Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and

acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml) This aqueous acetone solution was cooled to -30 °C and a (10 %) solution of aqueous sulphuric acid was added rapidly, stirred for 30 minutes and warmed to 0-2 °C. The product thus obtained was filtered at 0-2 °C, washed with cold-water (100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 89.0 %, water content 4-5 %).

Example 2

Step (i)

Preparation of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a chilled suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (5 gm) and (2-mercapto-5-phenyl-1,3,4-oxadiazolyl)-(Z)-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate (24.2 gm) prepared according to the procedure given in example (1) step (i) in tetrahydrofuran (40 ml) and water (5 ml), triethylamine (4.6 gm) was added drop-wise at 20±2 °C over 10-15 minutes and the resulting mixture was stirred at 30±2 °C for 6-8 hours. The progress of the reaction was monitored by HPLC. After completion of reaction, ethylacetate (100 ml) and water (75 ml) were added at 30±2 °C and stirred for 20 min. The aqueous layer was separated and washed with ethyl acetate (75 ml). To the aqueous layer, ethylacetate (150 ml) was added, cooled to 10 - 15 °C, and the pH was adjusted to 2.8-3.0 by 1:1 HCl solution in 25-30 min. To the separated ethylacetate layer, acetone (50 ml) and a methanolic potassium hydroxide solution (7.5 % w/v, 20 ml) were added dropwise in 25-30 min at 25 –27 °C and stirred for further 45 min. The resulting slurry was filtered,

washed with acetone (2 X 25 ml) and dried at 30-35 °C under vacuum to obtain the title compound (5.0 gm, HPLC Purity >99.0 %).

Step (ii)

Preparation of ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate

To a clear solution of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (250 gm) in aqueous acetonitrile (625 ml, 2:3), a solution of trimethylchlorosilane (94 gm) in acetonitrile (125 ml) was added drop wise at 60-65 °C. and the temperature was maintained at 65-68 °C for 33 minutes. Chilled acetone (2000 ml) having temperature -10 °C was added to the reaction mixture to reduce the temperature to 30 - 35 °C. A methanolic solution of ammonium acetate (93 gm, 100 ml) was added drop wise while cooling. The resulting mixture was diluted with acetone (3000 ml), cooled to 10 °C and stirred for 30 minutes at 10 ± 2 °C. The crystals thus obtained were filtered, washed with acetone and dried at 40-45 °C under vacuum to get ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (207 gm, HPLC quality 94.9 %).

Step (iii)

Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml). The pH of this aqueous acetone

solution was adjusted to 0.6 at 33-35 °C using a (10 %) solution of aqueous sulphuric acid. This solution was cooled rapidly to -10 °C and stirred for 30 minutes. The product thus obtained was filtered at -10 °C, washed with cold-water (100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 93.0 %, water content 4-5 %).

Example 3

Step (i)

Preparation of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a well stirred suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (50 gm) and (2-mercaptobenzothiazolyl)-(Z)-2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate (130 gm) in aqueous tetrahydrofuran solution (450 ml, 1:8), triethylamine (45 gm) was added drop wise at 25-30 °C and the resultant reaction mixture was stirred at 25-30 °C for 4-5 hours. After completion of reaction, water (1200 ml) and ethylacetate (1000 ml) were added, cooled to 20-25 °C and pH was adjusted to 2.0 to 2.3 by dilute hydrochloric acid (1:1, ≈ 82 ml) over 20 minutes. Ethylacetate layer was separated and the aqueous layer was extracted twice with ethylacetate (2 x 200 ml). The combined ethylacetate layer was treated with 15% brine solution. A methanolic potassium hydroxide solution (15 gm in 60 ml) was added dropwise to the clear ethylacetate solution at 25 to 30 °C. To the reaction mass, isopropyl ether (1000 ml) was added dropwise and stirred for 30 minutes. The product thus obtained was filtered, washed with isopropyl ether (200 ml) and dried at 45 °C under vacuum to get potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (167.5 gm, HPLC quality 93.6 % water content 8.1 % and assay 88-89 %).

Step (ii)

Preparation of ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate

To a clear solution of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (250 gm) in aqueous acetonitrile (625 ml, 2:3), a solution of trimethylchlorosilane (94 gm) in acetonitrile (125 ml) was added drop wise at 60-65 °C. and the temperature was maintained at 65-68 °C for 33 minutes. Chilled acetone (2000 ml) having temperature -10 °C was added to the reaction mixture to reduce the temperature to 30 - 35 °C. A methanolic solution of ammonium acetate (93 gm, 100 ml) was added drop wise while cooling. The resulting mixture was diluted with acetone (3000 ml), cooled to 10 °C and stirred for 30 minutes at 10 ± 2 °C. The crystals thus obtained were filtered, washed with acetone and dried at 40-45 °C under vacuum to get ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (207 gm, HPLC quality 94.9 %).

Step (iii)

Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml). The pH of this aqueous acetone solution was adjusted to 0.6 at 33-35 °C using a (10 %) solution of aqueous sulphuric acid. This solution was cooled rapidly to -10 °C and stirred for 30

minutes. The product thus obtained was filtered at -10 °C, washed with cold-water (100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 93.0 %, water content 4-5 %).

Example 4

Step (i)

Preparation of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate

To a well stirred suspension of 7-amino-3-vinyl-3-cephem-4-carboxylic acid (50 gm) and (2-mercaptobenzothiazolyl)-(Z)-2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetate (130 gm) in aqueous tetrahydrofuran solution (450 ml, 1:8), triethylamine (45 gm) was added drop wise at 25-30 °C and the resultant reaction mixture was stirred at 25-30 °C for 4-5 hours. After completion of reaction, water (1200 ml) and ethylacetate (1000 ml) were added, cooled to 20-25 °C and pH was adjusted to 2.0 to 2.3 by dilute hydrochloric acid (1:1, ≈ 82 ml) over 20 minutes. Ethylacetate layer was separated and the aqueous layer was extracted twice with ethylacetate (2 x 200 ml). The combined ethylacetate layer was treated with 15% brine solution. A methanolic potassium hydroxide solution (15 gm in 60 ml) was added dropwise to the clear ethylacetate solution at 25 to 30 °C. To the reaction mass, isopropyl ether (1000 ml) was added dropwise and stirred for 30 minutes. The product thus obtained was filtered, washed with isopropyl ether (200 ml) and dried at 45 °C under vacuum to get potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (167.5 gm, HPLC quality 93.6 % water content 8.1 % and assay 88-89 %).

Step (ii)

Preparation of ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate

To a clear solution of potassium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(trityloxyimino) acetamido]-3-vinyl-3-cephem-4-carboxylate (100.0 gm) in an aqueous acetonitrile (240 ml, 1:5), aqueous solution of hydrochloric acid (62 gm) was added dropwise at 60-65 °C and the temperature was maintained at 65-68 °C for 33 minutes. Chilled acetone (800 ml) having temperature -10 °C was added to the reaction mixture to reduce the temperature to 30 - 35 °C. A solution of ammonium acetate (37.2 gm) in methanol (40 ml) was added dropwise. The resulting mixture was diluted with acetone (1200 ml), cooled to 10 °C and stirred for 30 minutes at 10 ± 2 °C. The product thus obtained was filtered, washed with acetone and dried at 40-45 °C under vacuum to get ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate [80.5 gm, HPLC quality 95.45 %].

Step (iii)

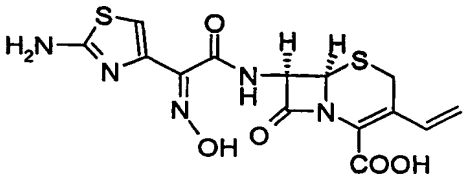
Preparation of (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid in amorphous hydrate form

Ammonium (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylate (20 gm) was added to a mixture of water (250 ml) and acetone (80 ml) and warmed to 33-35 °C. This aqueous solution was treated with activated charcoal and EDTA at 35 °C for 40 minutes. The carbon was filtered and the carbon bed was washed with water (70 ml). The pH of this aqueous acetone solution was adjusted to 0.6 at 33-35 °C using a (10 %) solution of aqueous sulphuric acid. This solution was cooled rapidly to -10 °C and stirred for 30 minutes. The product thus obtained was filtered at -10 °C, washed with cold-water

(100 ml) and dried at 40-45 °C under vacuum for 5-6 hours to get (Z)-7β-[2-(2-amino-4-thiazolyl)-2-(hydroxyimino)acetamido]-3-vinyl-3-cephem-4-carboxylic acid (6.0 gm, HPLC quality 93.0 %, water content 4-5 %).

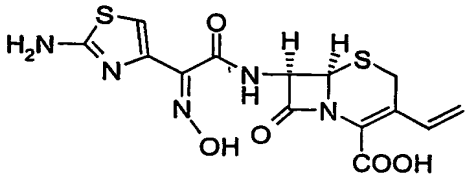
We claim :

1. Novel amorphous monohydrate of cefdinir of the formula (I).



(I)

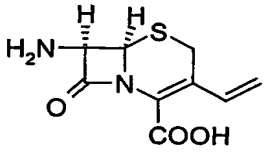
2. A process for the preparation of novel amorphous monohydrate of cefdinir of the formula (I)



(I)

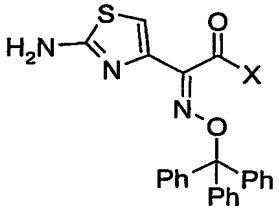
which comprises the steps of :

i) condensing 7-amino-3-cephem-4-carboxylic acid of the formula (XII)



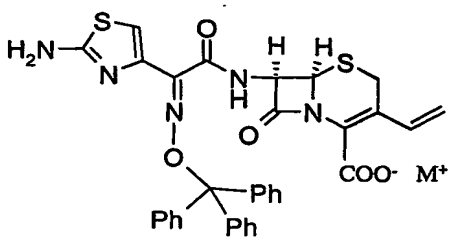
(XII)

with compound of the formula (XIII)



(XIII)

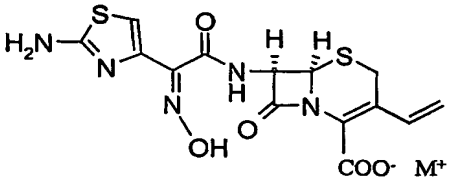
wherein X represents an activating group in the presence of a tertiary amine and an organic solvent, followed by treatment with a base to produce a salt of compound formula (XIV),



(XIV)

wherein M^+ is a counter ion,

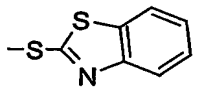
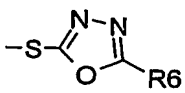
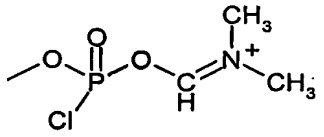
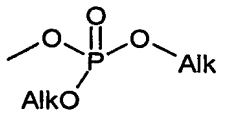
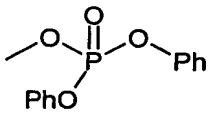
ii) deprotecting the compound of formula (XIV) to produce compound of formula (XV)



(XV)

wherein M^+ is a counter ion in the presence of an organic solvent and a base at a temperature in the range of room temperature to 80 °C and

iii) hydrolyzing the compound of the formula (XV) using an acid at low temperatures in the range of –40 to 0 °C in the presence of an organic solvent to produce novel amorphous monohydrate of cefdinir of the formula (I).

3. The process as claimed in claim 2, wherein the activation group represented by X is selected from ester, thioester, halogen atom such as chlorine, bromine, iodine,  ,  ,  ,  ,  , where R_6 represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl or a phenyl group; Alk group represents (C_1-C_4)alkyl group such as methyl, ethyl, n-propyl, iso-propyl, n-butyl or iso-butyl.

4. The process as claimed in claim 2, wherein the counter ion represented by M is selected from sodium, potassium, lithium, magnesium, ammonium, dicyclohexylamine, N,N'-dibenzylethylenediamine, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine or N,N-diisopropylamine.

5. The process as claimed in claim 2, wherein the tertiary amine used in step (i) is selected from triethylamine, N-methylpiperidine, N,N-diisopropylethylamine or trimethylamine.

6. The process as claimed in claim 2, wherein the organic solvent used in step (i) is selected from ethanol, methanol, isopropanol, THF, cyclohexanol, acetone, butan-2-one, acetonitrile, DMAc, water or a mixture thereof.

7. The process as claimed in claim 2, wherein the base used in step (i) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, ammonium acetate, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine or N,N-diisopropylamine.

8. The process as claimed in claim 2, wherein the base employed in step (ii) is selected from sodium hydroxide, sodium acetate, sodium 2-ethyl hexanoate, potassium hydroxide, ammonium hydroxide, ammonium acetate, calcium hydroxide, dicyclohexyl amine, N,N'-dibenzylethylenediamine diacetate, 1,8-diazabicyclo(5.4.0)undec-7-ene (DBU), 1,5-diazabicyclo(4.3.0)non-5-ene, N,N'-diphenylethylenediamine, 1,4-dizabicyclo(2.2.2)octane, N,N-diisopropylethylamine or N,N-diisopropylamine.

9. The process as claimed in claim 2, wherein the organic solvent used in step (ii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water or mixtures thereof.

10. The process as claimed in claim 2, wherein the hydrolysis in step (iii) is carried out by cooling the aqueous solvent solution to low temperatures and adding the acid rapidly to adjust the pH to precipitate the amorphous cefdinir.

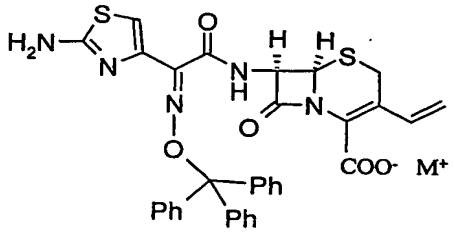
11. The process as claimed in claim 2, wherein the hydrolysis in step (iii) is carried out by adding the acid to adjust the pH and rapidly cooling the resultant solution to precipitate the amorphous cefdinir.

12. The process as claimed in claim 2, wherein the acid employed in step (iii) is selected from HCl, sulfuric acid, formic acid, acetic acid, benzenesulfonic acid, p-toluenesulfonic acid, naphthalenesulfonic acid, methanesulfonic acid or triflic acid.

13. The process as claimed in claim 2, wherein the organic solvent used in step (iii) is selected from acetone, 2-butanone, methanol, isopropanol, ethanol, THF, acetonitrile, DMAc, water or mixtures thereof.

14. The process as claimed in claim 2, wherein the compound of formula (I) obtained is a syn isomer.

15. A compound of compound formula (XIV),



(XIV)

wherein M^+ represents a counter ion.

Dated this twenty fourth (24th) day of February 2003

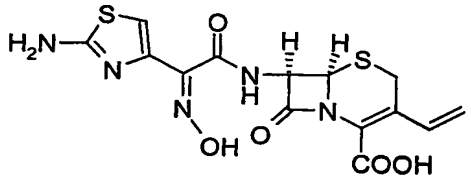
for Orchid Chemicals & Pharmaceuticals Ltd.,

Dr. C. B. Rao

Dy. Managing Director

Abstract

The present invention relates to novel amorphous monohydrate of cefdinir of the formula (I).

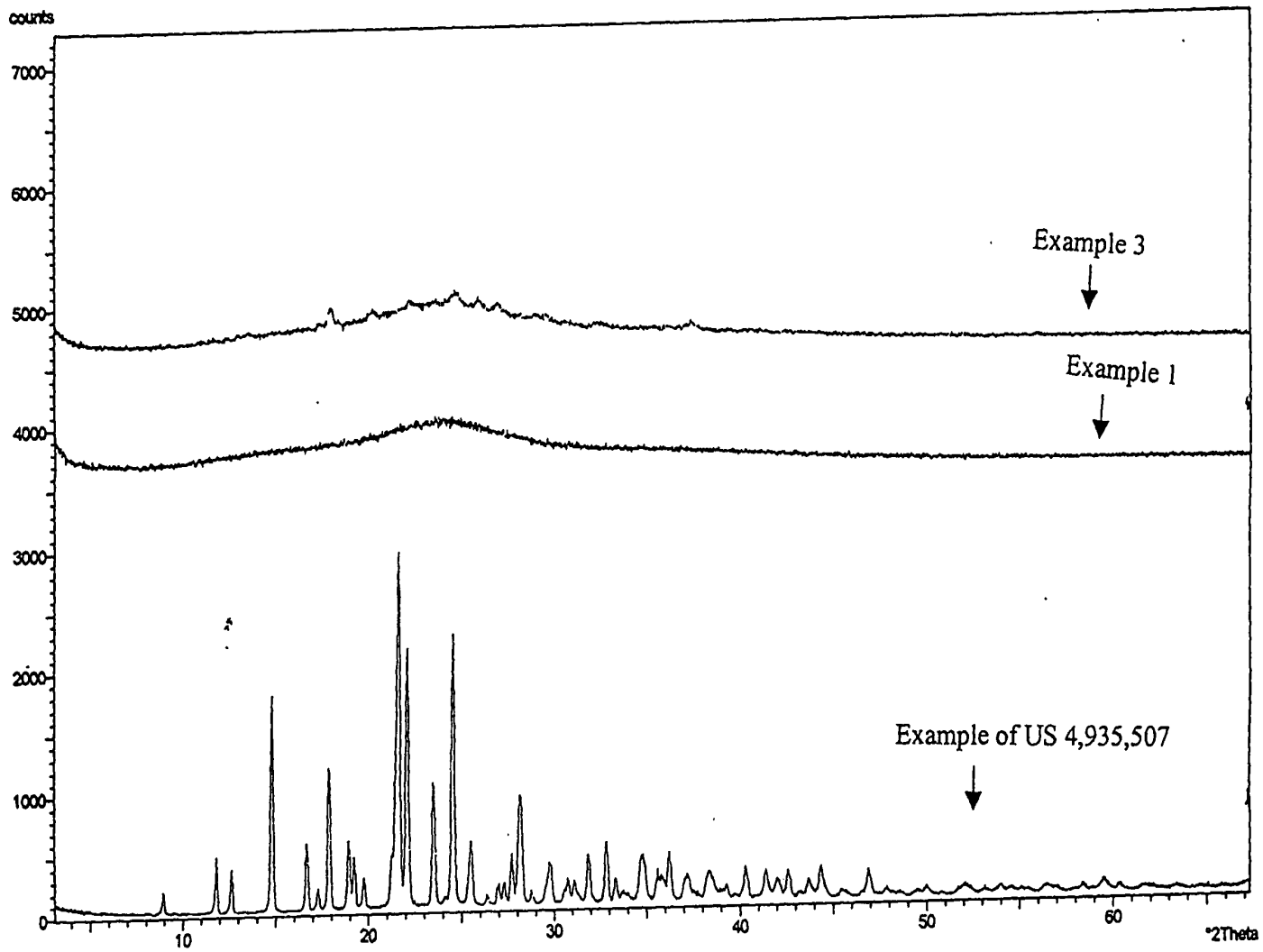


(I)

The present invention also provides a process for the preparation of the novel amorphous monohydrate of cefdinir of formula (I).

Complete Specification

X-ray difractogram



For Applicant